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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,116	07/03/2003	Colin M. Tice	A01386-US	3335

7590 11/14/2006

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/614,116	TICE ET AL.
	Examiner	Art Unit
	Ileana Popa	1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 08/24/2006.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 6-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 6-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 03 July 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claims 1-5 and 18 have been cancelled.

Claims 6-17 are pending and under examination.

Response to Arguments

Specification

3. The objection to the disclosure is withdrawn in response to Applicants' amendment filed on 08/24/2006.

Claim Rejections - 35 USC § 103

4. Claims 6-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Martinez et al. (Mol Gen Genet, 1999, 261: 546-552), in view of both Dhadialla et al. (Annu Rev Entomol, 1998, 43: 545-569) and Saez et al. (Proc Natl Acad Sci USA, 2000, 97: 14512-14517), as evidenced by Guan et al. (Journal of Combinatorial Chemistry, 2000, 2: 297-300) and Michelotti et al. (U.S. Patent No. 5,304,572) for the reasons of record set forth in the prior Office Action. Applicant's arguments filed 08/24/2006 have been fully considered but they are not persuasive.

Applicants traversed the instant rejection on the grounds that: (i) Martinez et al. teach multiple versions of inducible glucocorticoid gene expression systems in which the ability of a non-ecdysteroid inducer is low when compared to the constitutive 35SCaMV promoter, in which high inducer doses were necessary to achieve good induction levels, and in which the inducer was insoluble at the higher levels, (ii) the newly discovered compound of Dhadialla et al., i.e., DTBHIB, was unknown as a pesticide and its structure is not similar to that of the amidoketones of the present invention because it lacks a ketone group , an aromatic ring and substitutions recited in the instant claims, (iii) Saez et al. teach that over 100 pesticides were tested and, despite diverse chemistry, none of the compounds was effective to induce ecdysone-regulated gene expression. Saez et al. tested non-steroidal ecdysone agonists and found that they were not as good as the steroid PonA, and therefore they teach away from using non-steriodal ecdysone agonists, and (iv) the compound of Michelotti et al. is not a compound claimed in the instant invention and it is a fungicide, not a pesticide that functions to stimulate the insect ecdysone receptors. Applicants argue that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. Applicants assert that: (i) in the case of Martinez et al. there is no motivation to use non-steroidal ecdysone agonists because they were inefficient and in fact Martinez et al. might provide the motivation to design a different inducible system with high induction levels, low background and more soluble inducers, (ii) Saez et al. teach away from the use of non-steroidal ecdysone agonists because they state that they are not as active

as PonA, and (iii) one of skill in the art would not find any motivation to use the benzamides of Michelotti et al. as ecdysone agonists because they are known fungicides and structural features (i.e., the rpesnece of halides at the terminal carbon) that would not confer binding to ecdysone receptors. Due to these facts, Applicants submit that there is no motivation to combine these teachings. Additionally, Applicants argue that, given the difficulty in predicting the ability of a compound to act as a profivent ecdysone agonist (i.e., high induction, low background), it would require undue experimentation and low expectation of success to obtain the instant invention. Since they assert that the teachings as a whole fail to provide any motivation, Applicants request the withdrawal of the rejection.

Contrary to Applicants assertions, the prior art as a whole does provide the motivation required to achieve the instant invention for the following reasons:

First, Martinez et al. teach: (i) the usefulness of systems using chimeric receptors comprising the ligand-binding domain of insect ecdysone receptors for controlled gene expression in plants because gene expression form such promoters can be induced by using non-phytotoxic, non-steroidal edysone agonists, (ii) flexible and broad utility of such systems because of the availability of synthetic agonists compatible with agricultural use, together with the modular nature of nuclear receptors, and (iii) that, also other inducible systems are known, these systems are not compatible for agricultural use because the chemicals used as inducers are toxic for plants (p. 546, columns 1 and 2, p. 547, column 1, p. 550, column 1). Martinez et al. teach specific, dose-dependent activation in response to the non-steroidal ecdysone agonist RH5992

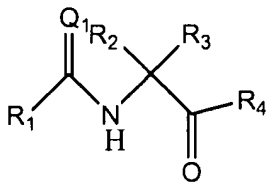
(Fig. 3 and 4). Although RH5992 solubility is low and cannot be used at a concentration higher than 100 μm, Martinez et al. clearly teach that induction of gene expression by RH5992 is higher (15-fold) when compared to other inducible systems such as dexamethasone / glucocorticoid receptor (6-fold) and definitely the background for the dexamethasone / glucocorticoid receptor system is higher, when same concentrations of inducers are used (p. 549, compare Fig. 2 and 3). Therefore, Martinez et al. clearly do not teach away from the instant invention and certainly do not provide a motivation to design a different inducible system. On the contrary, based on these teachings, one of skill in the art would be motivated to search for additional non-steroidal ecdysone agonists with improved solubility.

Second, Saez et al. teach ecdysone-inducible gene switch as a useful tool for modulating gene expression and that, although they must be used at high concentrations, a number of non-steroidal small molecule are able of activating the ecdysone system (Abstract, p. 14512, column 2, p. 14514, column 2, second full paragraph, p. 14516, Fig. 4). Saez et al. teach that, although these non-steroidal compounds are not as potent as ponA, they are manufactured in industrial quantities and animal experiments suggest that they are cleared slowly, therefore they might be useful in instances where sustained induction of gene expression is necessary (p. 14516, column 1, last paragraph). Saez et al. do not teach away from the instant invention. On the contrary, they do teach the ecdysone-inducible gene switch as very popular and the necessity of finding new sources of inducers, since the already established ones like MurA are difficult to be obtained (p. 14512, column 1 bridging

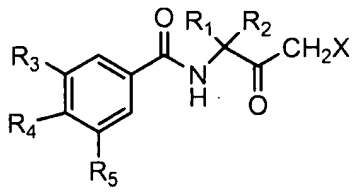
column 2). Therefore, based on the teachings of both Martinez et al. and Saez et al. one of skill in the art would be motivated to search for more efficient, readily available non-steroidal ecdysone agonists.

Third, while it is true that the DTBHIB of Dhadialla et al. was not tested as an insecticide, it is an ecdysone agonist with potency similar to RH-5849, known pesticide before the invention was made (p. 562 bridging p. 563). Applicants assert that DTBHIB is missing elements critical to the compounds of the instant invention, i.e., a ketone group, an aromatic ring and the substitutions recited in the claims. While this is true for the ketone group, DTBHIB (i.e., 3,5-di-tert-butyl-4-hydroxy-N-issobutyl-benzamide) has an aromatic ring with substitutions similar to those recited in the instant claims. For example DTBHIB comprises substituted phenyl (R1 in the instant claims), wherein the subsituents are tert-butyl and hydroxyl, i.e., C1-C6 alkyl and hydroxyl, as recited in the instant claims, and it also comprises isobutyl (R4 in the instant claims), i.e., C1-C6 alkyl, as disclosed in the instant claims. Although not identical, DTBHIB is very similar to the claimed compound, i.e., they have the same central core and moreover, both can be used as ecdysone agonists. Once the core of a desired compound is known, it is within the skills of the artisan to build combinatorial libraries around the central core by routine experimentation. Building combinatorial libraries is a common procedure in the art for the identifying of variants with improved activity (see Guan et al.). Based on these teachings and the teachings above, one of skill in the art would have been motivated to modify the method of Martinez et al. by using DTBHIB or its derivatives because DTBHIB was proven to be an efficient ecdysone agonist.

Fourth, while it is true that the compound of Michelotti et al. is a fungicide not and not a pesticide, it was well known in the art before the invention was made and its structure was very similar to the DTBHIB of Dhadialla et al. Moreover, the compound of Michelotti et al. is not toxic for plants and it is soluble (column 2 bridging column 3). Given these teachings and the teachings above, one of skill in the art would have been motivated to use it in the method of Martinez et al. The fact that the compound is used as a fungicide is irrelevant, since its structure is very similar to that of DTBHIB, a known ecdysone agonist (see the prior Office Action). Applicants assert that the compound of Michelotti et al. has structural features that would not confer binding to the ecdysone receptors, for example the presence of halides at the terminal carbon. First, it is not clear that Applicants have the evidence to make such an assertion. Second, a comparison between the compound of Michelotti et al. and the claimed formula I reveals that R4 of the claimed formula I can be CH_2X. Since the two compounds are identical (see below), it is not clear why the compound of Michelotti et al. would not bind the, while the claimed compound would bind the ecdysone receptors.



Claimed formula I, wherein R1 can be substituted phenyl Q1 can be O, and R4 can be (C1-C6) haloalkyl, for CH_2X, wherein X is a halide (see the instant claims)



The compound of Michelotti et al., wherein X can be a halide.

Therefore, given all the teachings above, one of skill in the art would have known to use combinatorial synthesis to generate libraries around the central core provided by DTBHIB or the compound of Michelotti et al. to search for the most efficient ecdysone agonists. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER